UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,725	11/16/2000	Ying Luo	RIGL-008CIP	6653

24353 7590 02/06/2004

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/715,725	Luo et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 3, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26-32* is/are pending in the application.

4a) Of the above, claim(s) *28 and 31* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26, 27, 29, 30, and 32* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed November 7, 2003 in response to the Office Action of August 8, 2003 is acknowledged and has been entered. Previously pending claims 27, 29, 32 have been amended. Claims 26-27, 29-30, 32 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

Claim Rejections - 35 USC § 112

4. Claim 27 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed August 8, 2003, section 5, pages 2-3.

Applicant argues that the rejection of claim 27 in paragraph 5 of the Office action and paragraph 11 of the office action is based on similar grounds under 35 USC 112, first paragraph so that both of these rejections will be addressed only once.

It is noted, however, that the grounds of rejection in the two paragraphs are quite different and therefore Examiner will address these rejections separately, first directly below and then below in the "New Grounds of Rejection" section.

As drawn to the rejection in paragraph 5, Applicant argues that the claims are amended to recite polypeptides having at least 95% sequence identity to the contiguous sequence set forth in SEQ ID NO:8. The claims are adequately described given Example 14 of the Synopsis of Application of Written Description Guidelines of March 1, 2000 because the fact pattern in Example 14 is very similar to that of the instant application. The argument has been considered but has not been found persuasive because Example 14 is drawn to an enzyme that catalyzes a particular

reaction and variants thereof that catalyze the same reaction, which reaction can be identified by screening for reaction products. The Example states that the single species disclosed is representative of the species claimed because all members must have at least 95% structural identity with the reference compound and because the screening assay identifies those which are capable of the specific catalytic activity, thus one of skill would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus. Unlike the cited example, the instant application is drawn to a protein that binds to an unidentified IAH and variants thereof having at least 95% structural identity with the reference compound. Neither the structure of the binding domain nor the IAH to which the reference compound binds is identified. It appears that the only screening assay taught in the specification is **not drawn** (emphasis added) to identifying variants that bind to IAH's but rather is drawn generally to the use of the proteins provided in the specification for screening purposes wherein the protein-protein interactions of the cell cycle proteins can be identified (see p. 42, lines 16-27). It is noted that binding to IAPs is not disclosed in this general teaching. Applicant further argues that the fact patterns of Example 14 and the instantly claimed invention are very similar in that (a) the present invention describes the sequence of a full length polypeptide, (b) describes that SEQ ID NO:8 has IAP binding activity, (c) contemplates but does not exemplify variants of SEQ ID NO:8, and (d) provides detailed methods of how IAP binding activity can be assayed and cites page 42, lines 16-27. This argument has been considered but has not been found persuasive because contrary to Applicant's argument and unlike Example 14, the activity of SEQ ID NO:8 is not specific to any one function, that is binding to

any one particular IAP of the whole universe of known IAPs and the specification does not provide detailed methods of determining IAP binding of the claimed variants, but rather as set forth above, provides general methods for the use of the proteins provided in the specification for screening purposes wherein the protein-protein interactions of the cell cycle proteins can be identified in a two hybrid system. It is again noted that binding to IAPs is not disclosed in this general teaching. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus that bind to SEQ ID NO:8, since the specification does not enlighten the artisan as to which of the numerous known and not yet discovered IAPs that SEQ ID NO:8 binds to, does not identify a structure within SEQ ID NO:8 that is associated with the binding function, the disclosure of the single specific amino acid sequence is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. The arguments have been considered but have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 101

5. Claims 26-27, 29-30, 32 remain rejected under 35 USC 101 for the reasons previously set forth in the paper mailed August 8, 2003, section 6, pages 3-11.

Applicant argues that the basis of the rejection appears to be that there is no teaching or evidence in the specification or in the art of record that any of the encoded proteins are in any way associated with apoptosis. This argument has been considered but has not been found persuasive because the basis of the rejection under 35 USC 101 is that there is no teaching or evidence in the specification or in the art of record that

SEQ ID NO:8 is in any way associated with the cell cycle or with apoptosis and there is no disclosure of why Applicant thinks that SEQ ID NO:8 binds to an IAP or is a cell cycle protein other than the 12.3% homology of the encoded ING2 to ING1, a known cell cycle protein and further, the specification does not teach what SEQ ID NO:8 is, what it does, does not teach a relationship to the cell cycle or to any particular disease. For the reasons of record, the homology of ING2 to ING1 does not provide a specific, well-established, substantial or credible utility to ING1, especially in view of the teaching of the specification that cell cycle proteins can be identified by substantial amino acid sequence identity or similarity (that is greater than 75% to about 98%) to the sequence of SEQ ID NO:8. If one were to give credence to this teaching, then ING1, although a known cell cycle protein, is not a cell cycle protein.

Applicant further argues that since experimental evidence shown in Figure 3 demonstrates that three isoforms of ING2 activate p53 which is a well known inducer of apoptosis, it reasonably follows that ING2 proteins activate an inducer of apoptosis and contrary to the Office's assertions, there is evidence in the specification that any of the encoded proteins are associated with apoptosis, they induce an activator of p53, a known inducer of apoptosis. The argument has been considered but has not been found persuasive because a review of the Figures originally filed with the specification reveals that Figure 3 shows the nucleic acid sequence of SEQ ID NO;3, encoding a cell cycle protein ING2, isoform 2. Further, although Applicant states that ING2A, ING2B and ING2C were assayed in p53 induction assays, it does not appear that ING2D, SEQ ID NO:8, was tested in p53 induction assay and it cannot be predicted from the information in the specification or the art of record whether or not SEQ ID

NO:8 would be an inducer of p53 activity. Solely in answer to Applicants arguments, given the known unpredictability of the art as taught by Zeremski et al, (JBC, 1999, 274, 32173-32181), submitted by Applicant with the instant response, it cannot be determined from the information in the specification whether or not SEQ ID NO:8 would be an activator or a suppressor of p53. If one were to assume, as Applicant suggests, that the activity of ING2 can be gleaned from that of ING1, it is clear that different isoforms of ING1 have different functions as Zeremski et al clearly teach that one isoform of ING1 cooperates with/activates p53 while the other inhibits p53 activity (see abstract). Further, Zeremski et al teach that a similar type of regulation involving alternative initiation leading to variability is found in other tumor suppressor genes namely BRCA1, APC and INK4, wherein this regulation is associated with the generation of proteins with different functions (p. 32180, col 1). In addition, even if it were to be disclosed that SEQ ID NO:8 does indeed activate p53, this would not provide support for the utility of the claimed invention because it is well known in the art that p53 is not limited to induction of apoptosis. It is noted that, only in response to Applicant's arguments, as taught by Zeremski et al, submitted by Applicant with the instant response, p53 controls not only sensitivity to apoptosis, but also replicative senescence, cooperation with dominant oncogenes and drug responses (see p. 32181, col 1) and thus further work must be done in order to established what, if anything association of SEQ ID NO:8 with p53 does and the invention does not have substantial utility. Further, even if it were to be found that SEQ ID NO:8 does activate p53, this would not provide specific utility for the claimed invention because this activity is clearly shared by many unrelated polypeptide structure sequences that have different

functions. Examiner takes note that myriad activators of p53 are known in the art. The arguments have been considered but have not been found persuasive and the rejection is maintained.

It is noted that Applicant does not address any of the issues raised except the apoptosis issue.

Claim Rejections - 35 USC § 112

6. Claims 26-27, 29-30, 32 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed August 8, 2003, section 7, pages 11-12.

As drawn to the rejection of claims 26-27, 29-30, 32 under 35 USC 112, first paragraph, Applicant apparently argues as set forth above. The arguments have been considered but have not been found persuasive for the reasons set forth previously and above.

7. Claims 27 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed August 8, 2003, section 9, pages 12-14.

Applicant argues that a skilled person, using the instant specification and what is known in the art could make and use the claimed ING2 variants without undue experimentation because Applicant has provided several examples of variants in their working examples wherein the variants range from 81.8% to 94.2% identity with SEQ ID NO:8 wherein all of these were identified in a two-hybrid assay using IAP protein as bait and three of these sequences were tested in p53 induction assays, since ING2 isoforms having as little as 81.8% identity to each other can effectively bind IAP and induce p53, a skilled person would reasonably expect ING2 variants with at least 95%

identity to have an activity similar to that of SEQ ID NO:8. The argument has been considered but has not been found persuasive as the claims are not limited to the disclosed variants nor are the claims limited to any one of the whole universe of known IAPs. Given the teachings of Bowie et al, Lazar et al, Burgess et al, given that no consensus binding sequence is taught, in the absence of guidance in the specification as to which residues are critical for the function as claimed, it cannot be predicted, now would it be expected that the broadly claimed polypeptides would function as claimed.

Applicant argues that adequate guidance as to which amino acids can be modified in an ING2 protein to maintain function, given the alignment of ING2 isoforms in Figure 11, given the known structure of ING1 protein, given that several regions are conserved between the various ING proteins, since the ING1 and ING2 proteins are functionally similar and contain several regions of conserved amino acids, including a large block of conserved amino acids at their C-termini, a skilled person would instantly recognize that these domains **may be** (emphasis added) be important for function of ING proteins and a skilled person would generally avoid making amino acid changes in these regions. The argument has been considered but has not been found persuasive, given that the homology between ING1 and ING2 is 12.8%, for the reasons previously set forth, it cannot be predicted that the function of the two proteins is the same. Further, the submitted reference by Zeremski et al, *Supra*, clearly teaches that different isoforms of ING1 have different functions, that is p53 activation and p53 inhibition and further teaches that a conserved C terminal sequence is a PHD finger domain which appears to be involved in the binding of ING1 to DNA (see p. 32180,

col 2). Although Applicant specifically points to the conserved C terminal domain as providing guidance for one of skill in the art, there is no suggestion or guidance in either the art of record or in the specification as originally filed as to which residues of SEQ ID NO:8 are involved with IAP binding or which IAP SEQ ID NO:8 binds so that one would be able to make the invention as claimed with a reasonable expectation of success. It appears that the skilled artisan is left with random experimentation to determine how to make the claimed invention. Random experimentation is undue. The arguments have been considered but have not been found persuasive and the rejection is maintained.

Applicant further argues that with the knowledge that ING1 and ING2 have apoptosis activity and have conserved domains, a skilled person would swap domains from ING1 to ING2, SEQ ID NO:8 with an expectation that the resultant protein would have apoptosis activity. The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claim as currently constituted, the claim is drawn to IAP binding activity, not to apoptosis activity.

Applicant argues that Zeremski et al confirms the conserved amino acids identified in Figure 11 and gives a domain name and function to the conserved C-terminal region. The argument has been considered but has not been found persuasive, the conserved C-terminal region disclosed in Zeremski et al is not drawn to a binding site for an IAP and is not drawn to the invention as claimed.

Applicant argues that since all the ING proteins shown in the figure have a conserved function, a skilled person would recognize that to make ING2 variants,

amino acids that correspond to conserved sequences should not be modified. The argument has been considered but has not been found persuasive because nothing in the specification as originally filed is drawn to an identification of the IAP binding site that must be conserved in order for the invention to function as claimed or to the nature of the IAP to which the ING2 variants would be expected to bind. In the absence of this information, for the reasons previously set forth and above, the claim is not enabled. The arguments have been considered but have not been found persuasive and the rejection is maintained.

It is noted that Applicant does not address the issue raised drawn to which IAP the claimed variants are to bind.

8. Claims 27 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed August 8, 2003, section 10, pages 14-16.

Because Applicant did not distinctly and specifically point out the supposed errors in the rejection under 35 USC 112, first paragraph, the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. Claim 27 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a variant or protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 that "binds to an inhibitor of apoptosis protein (IAP) has no clear support in the specification and the claims as originally filed. A review of the specification revealed support for the cell cycle protein provided herein binds to at least one inhibitor of apoptosis protein (p. 2, lines 15-19). Although the specification

repeatedly discloses general information about variants, in not a single instance is there a nexus made between any of the variants and binding to IAP. In particular, the specification teaches that variants typically exhibit the same qualitative biological activity as the naturally occurring analogue, although variants can also be selected which have modified characteristics (p. 13, lines 11-24). Nowhere is it suggested that the binding of the variant to IAP is a "qualitative biological activity". The subject matter claimed in claim 27 broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to submit point to the page and line number of the originally filed application wherein support for the newly added limitation can be found in order to obviate this ground of rejection.

Applicants arguments drawn to the rejection of claim 27 under 35 USC 112, first paragraph forth in the paper mailed August 8, 2003, section 11, page 16 are relevant to the instant rejection.

As drawn to the rejection in paragraph 11, Applicant argues that the claims are amended to recite polypeptides having at least 95% sequence identity to the contiguous sequence set forth in SEQ ID NO:8. The claims are adequately described given Example 14 of the Synopsis of Application of Written Description Guidelines of March 1, 2000 because the fact pattern in Example 14 is very similar to that of the instant application. The argument has been considered but has not been found persuasive because the rejection in paragraph 11 is drawn to the lack of clear support in the specification and the claims as originally filed for the limitation of a variant or protein comprising an amino acid sequence having at least 90% identity to SEQ ID NO:8 that "binds to an inhibitor of apoptosis protein (IAP). Likewise, there does not

appear to be support for the newly added limitation of a variant or protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 that "binds to an inhibitor of apoptosis protein (IAP)". Applicant is invited to submit point to the page and line number of the originally filed application wherein support for the newly added limitation can be found in order to obviate this ground of rejection.

10. All other objections and rejections recited in the paper mailed August 8, 2003 are withdrawn

11. No claims allowed.

12. Applicant's submission of the Zeremski et al reference prompted the new grounds of rejection and Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Yvonne Eyler, can be reached at (703) 308-3995.** The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.

Susan Ungar
Primary Patent Examiner
January 27, 2004